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Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : Mixture of antibiotics designated by A-21978, process for its production, their pharmaceutical compositions and producing microorganism.

Klassifikation / Classification / Classement : C 12 P 21/04

ENTSCHEIDUNG / DECISION

vom / of / du 25 June 1987

Anmelder / Applicant / Demandeur : Eli Lilly and Company

Patentinhaber / Proprietor of the patent / Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence :

EPÜ / EPC / CBE Articles 123 (2); 111 (1) EPC

Kennwort / Keyword / Mot clé : "Inadmissible modification"
"Remittal of the case"

Leitsatz / Headnote / Sommaire

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Case Number: T 161/86

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 25 June 1987

Appellant: ELI LILLY AND COMPANY
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Decision under appeal: Decision of Examining Division 023 of the European Patent Office dated 20 December 1985, refusing European patent application No 79 302 216.1 pusuant to Article 97(1) EPC.

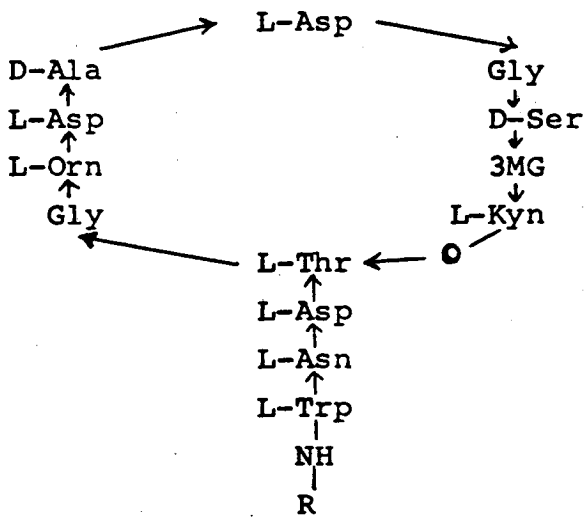
Composition of the Board:

Chairman: P. Lançon
Member: A. Nuss
Member: G. Paterson

Summary of Facts and Submissions

I. European patent application 79 302 216.1, filed on 15 October 1979 and published with publication number 10 421, claiming priority of the prior application of 16 October 1978, was refused by a Decision of the Examining Division of the European Patent Office dated 20 December 1985. The decision was based on Claims 1 to 11, received on 11 December 1984, and Claims 11 to 16, received on 27 July 1984. Since the two Claims 11 relate to different objects, Claims 11 to 16 should have been renumbered properly. Claim 1 reads as follows:

1. Antibiotic A-21978C factor C_0, which has the following tentative structural formula:



wherein 3MG represents L-threo-3-methylglutamic acid, and R is a C_{10} -alkanoyl moiety; and which has:

(a) a molecular formula of approximately $C_{72}H_{101}N_{17}O_{26}$;

(b) a molecular weight of approximately 1621; and which, in sodium salt form, has these characteristics:

(c) an approximate elemental composition of 52.07% carbon, 5.95% hydrogen, 12.73% nitrogen, 25.84% oxygen and 3.41% sodium;

(d) an infrared absorption spectrum in KBr pellet as shown in figure 5 of the drawings;

(e) upon hydrolysis yields the following amino acids:
aspartic acid, glycine, alanine, serine, threonine, tryptophan, ornithine, kynurenine, and 3-methyl-glutamic acid;

(f) is soluble in methanol, ethanol, propanol, butanol, dimethylformamide, dimethyl sulfoxide, dioxane, tetrahydrofuran, and water and in acidic and alkaline solutions, except at pH levels of below about pH 3.5; but is only slightly soluble or is insoluble in acetone, chloroform, diethyl ether, benzene, ethyl acetate, and hydrocarbon solvents;

(g) an R_f value of approximately 0.71 on reversed-phase silica-gel TLC in water:methanol:acetonitrile (45:15:40) which contains 0.2% pyridine and 0.2% acetic acid; and

(h) the following specific rotation:

$(\alpha)_D^{25}$ + 11.9° (c 0.7, H_2O);

or a salt of A-21978 factor C_0.

II. (a) The only reason for the refusal was that in the view of the Examining Division, the application has been amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC). In particular, a compound designated antibiotic A-21978 C factor C_0, having the tentative structural formula and the features (a) to (h), as stated in Claim 1, cannot be taken from the documents as filed.

Although the Examining Division considered it to be believable that the compound factor C_0 as originally prepared shows in the side chain between L-Asp and L-Trp an Asn residue and not, as originally tentatively disclosed, an Asp residue, the objection under Article 123(2) EPC had not been overcome by the Appellant, since he failed to show the identity of the compound as defined in Claim 1 and the compound factor C_0 as originally prepared, for the reason that the definition of the compound in the present claim is not a product-by-process claim definition, which would ensure such identity. Moreover, the structural formula quoted in Claim 1 is still a tentative one, and does not provide an unambiguous identity check.

(b) In addition, under point 4 of the reasons for the decision, the Examining Division expressed some doubt whether process Claim 11, received on 11 December 1984, insofar as it relates to the use of suitable mutants of the strain NRRL 11379, is allowable under Article 83 EPC. It was, however, stated that this

matter, made in the form of "remarks", was raised for the first time by the Examining Division and did not form part of the arguments used in deciding the rejection under Article 97 EPC.

III. On 18 February 1986, the Appellant lodged an appeal against this decision by telex, which was confirmed in a letter received the next day. The appeal fee was received in due time. The grounds for appeal, received on 19 April 1986, were essentially as follows:

The claimed antibiotic compounds (six in total) can be isolated by conventional means from the fermentation broth produced by submerged aerobic fermentation of Streptomyces roseosporus NRRL 11379. These related cyclic polypeptide antibiotic factors, designated A-21978C factors, are characterised in detail in the specification, not only by means of structural formulae, but also by parameters customarily used in the art to identify antibiotic factors.

After the application had been filed, it was found that the originally indicated structures were incorrect, in particular, one of the amino acid residues had been wrongly named, the reason therefore being that the penultimate amino acid residue is derived from asparagine rather than aspartic acid as had originally been thought. Furthermore, the alkanoyl moiety in the structure of the C_5 factor was found to be C_{12} alkanoyl and not C_{13} alkanoyl as indicated in the original description.

The tentative formulae given in the original application were based on the best available information at the time it was drafted, and methods and equipment at that time did not permit a more definitive assignment of structure.

However, when trying to correct the originally filed structures, the Examining Division could foresee but one possibility, namely that the claims should be converted to product-by-process claims.

IV. Together with the Grounds of Appeal, the Appellant had filed six different sets of claims (claim sets 1 to 6 received on 19 April 1986). In a subsequent letter received on 3 June 1986, he restricted his request to claim set 4 (Claims 1 to 11). The same letter contained some minor amendments to be made in Claims 2, 5 and 6 of this set.

The Appellant requests that the appealed decision be set aside and that a patent be granted on the basis of this version of the claims.
New Claim 1 reads as follows:

1. A cyclic polypeptide antibiotic designated A-21978C factor C_0, obtainable by isolation from a fermentation broth produced by cultivating Streptomyces roseosporus NRRL 11379 or a mutant thereof, having a terminal C_{10} -alkanoyl group, and having, in sodium salt form, these characteristics:

   (a) an approximate elemental composition of 52.07% carbon, 5.95% hydrogen, 12.73% nitrogen, 25.84% oxygen and 3.41% sodium;

   (b) an infrared absorption spectrum in KBr pellet as shown in Figure 5 of the drawings;

(c) upon hydrolysis yields 4 moles of aspartic acid, 2 moles of glycine, 1 mole of alanine, 1 mole of serine, 1 mole of threonine, 1 mole of tryptophan, 1 mole of ornithine, 1 mole of kynurenine, and 1 mole of 3-methylglutamic acid;

(d) is soluble in methanol, ethanol, propanol, butanol, dimethylformamide, dimethyl sulfoxide, dioxane, tetrahydrofuran, and water and in acidic and alkaline solutions, except at pH levels of below about pH 3.5; but is only slightly soluble or is insoluble in acetone, chloroform, diethyl ether, benzene, ethyl acetate, and hydrocarbon solvents;

(e) an R_f value of approximately 0.71 on reversed-phase silica-gel TLC in water: methanol: acetonitrile (45:15:40) which contains 0.2% pyridine and 0.2% acetic acid; and

(f) the following specific rotation:

$$(\alpha)_D^{25} + 11.9° \ (\underline{c}\ 0.7,\ H_2O);$$

or a salt of A-21978 factor C_0.

Claims 2 to 6 are similar claims corresponding to five additional, closely related cyclic polypeptide antibiotics designated A-21978C factors C_1, C_2, C_3, C_4 and C_5 having their own characteristics (a) to (f). Claims 2 to 4 contain two more characteristics (g) and (h).

Claims 7 to 11 are identical with the last five claims of the set received on 11 December 1984 and on which the decision of the Examining Division was based.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. The Board considers that the Decision of the Examining Division regarding the previous Claim 1 was correct.

3. The effective Claim 1 has now, however, been worded in the way suggested by the Examining Division in the form of a product-by-process claim, including only such characteristics which need not be corrected and which were, therefore, not in dispute. In particular, the contested (corrected) tentative structural formula has been deleted from the claim, together with additional characteristics relating to corresponding molecular formula and molecular weight.

   It is perfectly clear from the original description that antibiotic A-21978C factor C_0 may be obtained in the way indicated in the first part of the claim (cf. in particular, page 2, line 28 to page 3, line 20 and page 4, lines 1 to 9). Moreover, the figures of present characteristic (a) correspond to the elemental composition actually found (not calculated) for this factor and which is disclosed in table II on page 8 of the original description. Those of characteristic (c) may be found on page 4 of the description (see in particular, lines 9 to 21).

The terminal alkanoyl group and the remaining characteristics (b) and (d) to (f) may be found in the original disclosure too (cf. in particular, original Claim 3).

4. The same applies to Claims 2 to 6 relating to further antibiotic A-21978C factors C_1 to C_5, except that for these factors the characteristics (b) and (d) to (f), together with additional characteristics (g) and (h) for factors C_1 to C_3, are based on corresponding original claims (cf. in particular, original Claims 4 to 8) and that in Claim 6 the expression "terminal fatty acid acyl group" replaces the incorrect "C_{13}-alkanoyl moiety" which is now believed to be a C_{12}-alkanoyl group. In connection with the latter, it is to be noted that the original description leaves no doubt that all six antibiotics, i.e. factors C_0 to C_5 bear a terminal fatty acid acyl group (cf. in particular, page 4, lines 1 to 9 and page 6, line 19).

5. Finally, the remaining Claims 7 to 11 are identical with Claims 7 to 11, received on 11 December 1984. These claims are also adequately supported by the original disclosure of the application (see in particular, page 2, line 1 to page 3, line 11 of the original description and original Claims 9 to 15). This was not a matter of dispute.

6. Therefore, since present Claims 1 to 11 contain only subject-matter which derives directly and unambiguously from the original application, they all satisfy the requirements of Article 123(2) EPC.

7. In view of the fact that the application was finally refused with the explicit agreement of the Appellant (see letter received on 23 May 1985) in order to specifically allow the purely formal question of admissible amendments of the

claims under Article 123(2) EPC to be dealt with by the Board of Appeal, there is no reason for the Board to decide on other questions pending at this stage of the proceedings.

In the Board's view the proper procedure in this circumstance is that any outstanding matters should now be further pursued by the first instance. Thus, the Board considers that it is inappropriate to investigate the additional remarks made by the Examining Division under point 4 of the reasons for the decision, and makes use of its power under Article 111(1) EPC to remit the case to the Examining Division for further prosecution.

Order

For these reasons, it is decided that:

1. The decision of the Examining Division of 20 December 1985 is set aside.

2. The case is remitted to the Examining Division for further substantive examination on the basis of claim set 4, containing Claims 1 to 11, received on 19 April 1986 and amended with respect to Claims 2, 5 and 6 in the way indicated in Appellant's letter, received on 3 June 1987.

The Registrar

The Chairman